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10/616,323	07/09/2003	Laurence A. Cole	MBHB 03-411-A	1369

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COLEMAN SUDOL SAPONE, P.C.
714 Colorado Avenue
Bridgeport, CT 06605-1601

EXAMINER	
REDDIG, PETER J	
ART UNIT	PAPER NUMBER
1642	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/11/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/616,323	COLE, LAURENCE A.	
	Examiner	Art Unit	
	Peter J. Reddig	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 November 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16* is/are rejected.

7)☒ Claim(s) *1,5,9 and 16* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *09 July 2003* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6/7/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The Amendment filed November 2, 2006 in response to the Office Action of May 30, 2006 is acknowledged and has been entered.

2. Previously pending claims 17-45 have been cancelled and claims 1 and 13 have been amended.

3. Claims 1-16 are currently being examined.

4. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

5. The following rejections are being maintained:

Claim Rejections - 35 USC 102

6 Claims 1, 4-8, 10 and 11 remain rejected under 35 USC 102 for the reasons previously set forth.

Applicant argues that the claims are not anticipated by the method of Kobata simply because Kobata teaches measuring a variant of hCG which is not ITA, as that term has been defined in the specification. Applicant argues that, in particular, Kobata is directed to measuring N-linked glycosylated variant of hCG, not O-linked glycosylated variant hCG as in the present invention. Applicant argues that there are a number of glycosylated variants, it is the type of variant which will determine the accuracy of the assay and whether or not invasive trophoblast cells exist in a sample. Applicant argues that Kobata is measuring N-linked glycosylation of hCG, which is much less reliable than the measurement of O-linked glycosylation of hCG or ITA.

Applicant's argument has been considered, but has not been found persuasive because neither the definition of ITA nor the claims are limited to the O-linked glycosylated variant hCG. Thus, applicant is arguing limitations not recited in the claims. It is noted that Applicant's argument that measuring N-linked glycosylation of hCG is much less reliable than the measurement of O-linked, glycosylated hCG raises the question of enablement of the claims as currently set forth.

Applicant argues that the definition of ITA, the O-linked glycosylated variant which is measured in the present invention, is set forth in the specification at page 5, in the second full paragraph. Applicant argues that this is the variant which Applicant has focused on and to which the present invention is directed to measuring. Applicant argues that, this is not what Kobata is measuring. Applicant argues that, in contrast to the present method, Kobata only deals with and measures N-linked glycosylated hCG, not the O-linked glycosylated hCG which is measured in the present invention.

Applicant's argument has been considered, but has not been found persuasive because a review of the second full paragraph on page 5 revealed that the specification teaches that:

> "ITA" is an abbreviation for invasive trophoblast antigen, also known as hyperglycosylated hCG. ITA is, therefore, a variant of regular hCG, comprising additional side chains of sugars on the N-linked and O-linked sugar chains compared with regular hCG. These additional sugar side chains comprise N-acetylglucosamine, galactose and sialic acid and make the molecule considerably larger in size.

Thus the claims as currently set forth are not limited to the N-linked form of ITA and applicant is arguing limitations not found in the claim.

Applicant argues that the paper by Valmu, et al., "Site-specific glycan analysis of human chorionic gonadotropin 13-subunit from malignancies and pregnancy by liquid chromatography-

electrospray mass spectrometry", Glycobiology Advance Access, July 31, 2006, clearly shows that the O-linked glycosylated hCG variant ITA, which is measured in the present method, is distinguishable over the N-linked glycosylated hCG which is measured by Kobata. Applicant argues that not only does the enclosed paper show the distinction between the N-linked and O-linked glycosylated variants of hCG, but also points to the superiority of measuring ITA, which is the only significant and consistent change in choriocarcinoma. Applicant argues that, Kobata, clearly is directed to measuring a different hCG variant and the disclosed method clearly does not anticipate the present invention.

Applicant's argument has been considered, but has not been found persuasive because the claims are not limited to the O-linked glycosylated variant hCG. Thus, applicant is arguing limitations not recited in the claims. Again, Applicant's argument that measuring N-linked glycosylation of hCG is much less reliable than the measurement of O-linked, glycosylated hCG raises the question of enablement of the claims as currently set forth. Applicant can obviate the instant rejection by clearly directing the claims to the O-linked form of ITA that functions as claimed, given that support for such amendment can found in the specification as originally filed.

New Grounds of Rejection and Objection

Drawings

7. The drawings are objected to as failing to comply with 37 CFR 1.84(p)(5) because they do not include the following reference sign(s) mentioned in the description: Figure 5, see p. 29, line 14. Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. Each drawing sheet submitted after the filing date of

an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Claim Objections

8. Claims 9 and 16 are objected to because of the following informalities: The word placenta is misspelled. Appropriate correction is required.

9. Claim 5 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Claim 1 recites "the total amount of hCG" and Claim 5 recites "total hCG". Thus, claim 5 fails to further limit claim 1.

Claim Rejections - 35 USC § 112

10. Claims 1-11 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: Determining that invasive trophoblast cells are absent from the sample if the percentage of the total amount of hCG that is ITA is less than 30%.

11. Claims 1-16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "amount" in claim claims 1 and 12 is a relative term which renders the claim indefinite. The term "amount" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Does the term "amount" refer to all of the ITA in the sample or a portion of the ITA in the sample? Thus the metes and bounds of the claims cannot be determined.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims 1-16 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 1-11 are drawn to a method of detecting the presence or absence of invasive trophoblast cells in a biological sample comprising the steps of: a. obtaining a biological sample from a patient; b. measuring the total amount of hCG in the biological sample; c. measuring an amount of ITA in the biological sample; d. determining the percentage of the total amount hCG that is ITA, e. and determining that invasive trophoblast cells are present in the sample if the percentage is 30% or greater. Claims 12-16 are drawn to a method of diagnosing quiescent gestational trophoblastic disease in a patient having persistently low hCG titers if the percentage of hCG that is ITA is less than 30%.

The specification teaches that serum and urine samples were analyzed using specialized "in house" assays, in addition to commercial hCG assays, see p. 14, lines 9-22.

Applicant argues, in the remarks of 11/02/2006, that "In particular, Kobata is directed to measuring N-linked glycosylated variant of hCG, not O-linked glycosylated variant hCG as in the present invention. Inasmuch as there are a number of glycosylated variants, it is the type of variant which will determine the accuracy of the assay and whether or not invasive trophoblast cells exist in a sample. In the case of Kobata, Kobata is measuring N-linked glycosylation of hCG, which is much less reliable than the measurement of O-linked glycosylation of hCG or ITA. Note that the definition of ITA, the O-linked glycolsylated variant which is measured in the present invention, is set forth in the specification at page 5, in the second paragraph. This is the variant which Applicant has focused on and to which the present invention is directed to measuring." As set forth above, a review of page 5, second paragraph defines of ITA as a variant of regular hCG, comprising additional side chains of sugars on the N-linked and O-linked sugar chains compared with regular hCG. It is clear from the teaching of the specification that the invention is not limited to the O-linked variant and it does not appear that anything in the specification or claims specifically directs the practitioner to any O-linked variant.

One cannot extrapolate the teachings of the specification to the enablement of the claims because the specialized "in house" assays used to measure hCG/ITA are not described and the applicant argues that the measurement of N-linked ITA is much less reliable than measuring O-linked ITA.

The specification provides neither information nor guidance on how to make and use the specialized "in house" assays for measuring hCG/ITA. Additionally, the specification provides neither information nor guidance on how to measure ITA as claimed when the measurement of N-linked ITA is much less reliable than measuring O-linked ITA. The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict that the invention would function as claimed with a reasonable expectation of success. For the above reasons, it appears that undue experimentation would be required to practice the claimed invention.

13. Claims 1-11 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to a method of detecting the presence or absence of invasive trophoblast cells in a biological sample comprising the steps of: a. obtaining a biological sample from a patient; b. measuring the total amount of hCG in the biological sample; c. measuring an amount of ITA in the biological sample; d. determining the percentage of the total amount hCG that is ITA, e. and determining that invasive trophoblast cells are present in the sample if the percentage is 30% or greater.

The specification teaches that hCG (human chorionic gonadotropin) is a hormone that increases during pregnancy and is commonly used to confirm pregnancy and as a marker for

gestational trophoblastic disease and germ cell tumors. The specification teaches that if a woman is not pregnant but has an increased level of hCG it may indicate the presence of a gestational trophoblastic tumor, see p. 1 lines 20-23.

The specification teaches that "ITA" is an abbreviation for invasive trophoblast antigen, also known as hyperglycosylated hCG, see p. 5 lines 10-11.

The specification teaches that the USA hCG References Service observed 80 cases of persistent low levels of hCG, whether with history of hydatidiform mole or gestational trophoblastic disease (quiescent gestational trophoblastic disease) or with history of only pregnancy (unexplained elevated hCG). The specification teaches that total hCG and ITA were measured in 53 of the 80 cases with persistent low hCG levels (Tables 7 and 5). The specification teaches that ITA was not detected (<2 IU/L) in 49 of the 53 cases with persistent low levels of hCG, and accounted for no more than 21% (<30%) of the total hCG in the remaining four cases. Additionally, the specification teaches that in sera from 13 additional patients with proven choriocarcinoma, only high proportions of ITA (>30% of total hCG) were detected (Table 4). The specification teaches that as described in Tables 7 and 3, in 7 of the 80 cases with persistent low levels of hCG, malignant disease developed and ITA results were 57% to 100% of total hCG (Table 4). The specification teaches that, putting these cases together, ITA accounted for more than 30% of total hCG immunoreactivity in 20 of 20 malignant cases, and in none of the 53 individuals with persistent elevated hCG (non-invasive disease), see p. 30, lines 6-27.

One cannot extrapolate the teachings of the specification to the enablement of the claims because hCG, and its ITA variant, is a secreted hormone and one would not predict

that measuring the levels of a secreted hormone in a biological sample would indicate the presence or absence of the cells that secreted the hormone **in the sample.**

In particular, Norman et al. (Ann. Clin. Biochem.; 1990; 27:183-194, IDS item) teach the hCG is a secreted hormone that can be found in the blood and urine, see p. 183, left column and p. 186 left column. However, neither Norman et al nor the specification as originally filed teaches that cells are found in urine or blood thus, one of skill in the art would not predict that detection of a secreted protein in a biological sample would indicate the presence or absence of the cells **in the sample** that secreted them because when the hCG or ITA is secreted they are no longer associated with the cell that produced them. Thus additional experimentation would be required to identify markers that are constitutively and permanently associated with invasive trophoblast cells to confirm their presence or absence **in the sample.**

The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict that the invention would function as claimed with a reasonable expectation of success. For the above reasons, it appears that undue experimentation would be required to practice the claimed invention.

14. Claim 12 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claim is drawn to a method of diagnosing quiescent gestational trophoblastic disease in a patient having persistently low hCG titers if the percentage of hCG that is ITA is less than 30%.

The specification teaches that "low level" of hCG is detected where the concentration of hCG is 2 to 200 IU/L. The specification teaches that a "persistently" low level of hCG is detected where a low level of hCG is detected in biological samples obtained from a single patient at subsequent time intervals, for example, at weekly, monthly, or bi-monthly time intervals.

The specification teaches that the USA hCG References Service observed 80 cases of persistent low levels of hCG, whether with history of hydatidiform mole or gestational trophoblastic disease (quiescent gestational trophoblastic disease) or with history of only pregnancy (unexplained elevated hCG). The specification teaches that in 7 of the 80 cases (those referred for a second time to the USA hCG Reference Service) after periods of 2 months to 6 years of persistent low hCG levels, hCG results rapidly rose, indicating active disease. The specification teaches that in one case placental site trophoblastic tumor was detected and in six cases gestational trophoblastic disease choriocarcinoma was diagnosed and treated. The specification teaches that this observation indicated that persistent low levels of hCG may be a pre-malignant condition, see p. 30, lines 6-14. Furthermore, the specification teaches that the percent ITA is an accurate indicator of invasive malignant trophoblastic disease, with use in differentiating persistent low levels of hCG from malignant disease, see p. 30 lines 27-29.

One cannot extrapolate the teachings of the specification to the enablement of the claims because one could not diagnose the quiescent gestational trophoblastic disease from a patient having persistently low hCG titers if the percentage of hCG that is ITA is less than 30% because

the level of hCG is normally low in healthy individuals and the percentage of hCG that is ITA is also normally low in healthy individuals. Thus, without prior diagnosis of gestational trophoblastic disease, one of ordinary skill in the art could not predict that quiescent gestational trophoblastic disease was present.

In particular Sturgeon and McAllister (Ann. Clin. Biochem. 1998: 35: 460-491, IDS item) teach that the upper reference limit for hCG in women range from 3 to 5 U/L of hCG in women, see p. 463, right column. Additionally Sturgeon and McAllister teach that the upper reference limit for men under 50 is 0.7-1.0 U/L, increasing to 2-3 U/L in older men, see p. 466, left column. Additionally, Elliot et al. (Endocrine, 1997, 7:15-32, IDS item) teach that changes in the glycosylation of hCG have been observed during pregnancy and choriocarcinoma, see para bridging p. 16 and 17. Furthermore, Cole et al. (Clinical Chemistry, 2001 47:308-315, IDS item) teach that hyperglycosylated hCG, nicked hCG, hCG minus C-terminal peptide, asialo hCG, and free β subunit are either unique to trophoblastic diseases or more abundant in trophoblastic disease samples, see p. 311, right column.

Given that the levels of hCG are normally low in healthy individuals and that elevated glycosylation of hCG has only been reported to occur in pregnancy and cancer, one of ordinary skill in the art could not predict if a patient with persistently low hCG titers and a percentage of hCG that is ITA less than 30% had quiescent gestational trophoblastic disease without any a prior diagnosis of gestational trophoblastic disease because one would expect that any healthy, non-pregnant individual would have low hCG and ITA levels.

The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and

no evidence has been provided which would allow one of skill in the art to predict that the invention would function as claimed with a reasonable expectation of success. For the above reasons, it appears that undue experimentation would be required to practice the claimed invention.

15. If applicant were able to overcome the rejections set forth above, claims 1-16 would still be rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of detecting the presence or absence of invasive trophoblast cells in a biological sample by determining the percentage of the total amount of hCG that is ITA and determining that invasive trophoblast cells are present in the sample if the percentage is 30% or greater and a method of diagnosing quiescent gestational trophoblastic disease in a patient if the percentage of hCG that is ITA is less than 30%, **wherein hCG consists of intact hCG (α and β subunit) or free β hCG subunit,** does not reasonably provide enablement for a method of detecting the presence or absence of invasive trophoblast cells in a biological sample by determining the percentage of the total amount of hCG that is ITA and determining that invasive trophoblast cells are present in the sample if the percentage is 30% or greater and a method of diagnosing quiescent gestational trophoblastic disease in a patient if the percentage of hCG that is ITA is less than 30%. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are broadly drawn to a method of detecting the presence or absence of invasive trophoblast cells in a biological sample by determining the percentage of the total

amount of hCG that is ITA and determining that invasive trophoblast cells are present in the sample if the percentage is 30% or greater and a method of diagnosing quiescent gestational trophoblastic disease in a patient if the percentage of hCG that is ITA is less than 30%.

This means that measurement of **any** form of hCG and determining the percentage that is ITA will detect the presence or absence of invasive trophoblast cells or diagnose quiescent gestational trophoblastic disease in a patient.

The specification teaches as set forth above.

Additionally, the specification teaches that the term "hCG" is used herein to refer to any subunit of hCG, fragment of hCG, intact hCG, an isoform of hCG, a modified hCG molecule, total hCG, or any combination thereof see para bridging p. 5 and 6.

The specification teaches that "total hCG" comprises regular hCG and all forms of hCG, including free α and β subunits of hCG and β core fragment of hCG, as well as hCG isoforms such as ITA, see p. 6, lines 4-6

The specification teaches that total hCG was measured using the DPC Immunilite test when determining the percentage of hCG that is ITA, see p. 30, lines 15-17.

One cannot extrapolate the teachings of the specification to the scope of the claims because no nexus has been established between all forms of the broadly claimed hCG, ITA, and detecting the presence or absence of invasive trophoblast cells or diagnosis of quiescent gestational trophoblastic disease in a patient and 1) the unpredictability of measuring hCG is well known art and the hCG test used in the specification does not detect all forms of hCG 2) the unpredictability of biochemistry is well known in the art.

1) As drawn to the unpredictability of measuring hCG levels, Cole et al. (Clinical Chemistry, 2001 47:308-315, IDS item) teach that patients with trophoblastic diseases produce ordinary and irregular forms of human chorionic gonadotropin that are recognized to differing extents by automated immunometric hCG (or hCGβ) assays. Cole et al. teach this has led to low or false-negative results and misdiagnosis of persistent disease. Furthermore, Cole et al. also teach false-positive hCG immunoreactivity has also been detected; leading to needless therapy for trophoblastic diseases, see Abstract.

Additionally, Cole et al. teach that the DPC test used by the inventor is a chemiluminescence test, using a capture antibody and a tracer antibody directed toward different regions of the core of hCG β subunit, but does not detect free α subunit, see, p. 309, left column and p.314, right column.

Given the known unpredictability of measuring hCG levels and given that the test used in the specification does not detect all of the broadly claimed forms of hCG one of ordinary skill in the art could not predict that measuring any hCG, as broadly claimed, would allow the detection of the presence or absence of invasive trophoblast cells or the diagnosis of quiescent gestational trophoblastic disease without additional knowledge about the roles of the broadly hCGs in invasive trophoblast cells and gestational trophoblastic disease.

2) As drawn to the unpredictability of protein biochemistry, Bowie et al (Science, 1990, 257:1306-1310) teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the instructions of the genome and further teaches that the problem of predicting protein structure from sequence data and in

turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex (col 1, p. 1306). Bowie et al further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (col 2, p. 1306). The sensitivity of proteins to alterations of even a single amino acid in a sequence are exemplified by Burgess et al (J of Cell Bio. 111:2129-2138, 1990) who teach that replacement of a single lysine reside at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein and by Lazar et al (Molecular and Cellular Biology, 1988, 8:1247-1252) who teach that in transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen. These references demonstrate that even a single amino acid substitution will often dramatically affect the biological activity and characteristics of a protein. In view of the undefined alterations in the hCG protein contemplated in the specification and claimed, the function of the broadly claimed hCG proteins would not be expected to be the same as that of an unaltered hCG protein and the relationship of the broadly claimed hCG proteins to invasive trophoblast cells and quiescent trophoblastic disease could not be extrapolated to those seen with the hCG protein studied in the examples with a reasonable expectation of success.

Clearly, given the teachings of Bowie et al, Lazar et al, and Burgess et al the effects of undefined changes in the hCG polypeptide could not be predicted. Thus, it would take undue experimentation for one of ordinary skill in the art to practice the invention as claimed.

Applicant is reminded that MPEP 2164.03 teaches "the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability of the art. In re Fisher, 428 F.2d 833, 166 USPQ 18, 24 (CCPA 1970) the amount of guidance or direction refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly state in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as how to make and use the invention in order for it to be enabling. Given only lack of guidance in the specification, no one skilled in the art would accept the assertion that the claimed invention would function as contemplated or as claimed based only on the information in the specification and that known in the art at the time the invention was made.

The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict that the invention will function as contemplated or claimed with a reasonable expectation of success. For the above reasons, it appears that undue experimentation would be required to practice the claimed invention.

16. Claims 1-16 are rejected under 35 USC 112, first paragraph, as lacking an adequate written description in the specification.

Claims 1-16 are broadly drawn are drawn to a method of detecting the presence or absence of invasive trophoblast cells in a biological sample by determining the percentage of the total amount of hCG that is ITA and determining that invasive trophoblast cells are present in the sample if the percentage is 30% or greater and a method of diagnosing quiescent gestational trophoblastic disease in a patient if the percentage of hCG that is ITA is less than 30%. It is noted that the specification teaches that the term "hCG" is used herein to refer to any subunit of hCG, fragment of hCG, intact hCG, an isoform of hCG, a modified hCG molecule, total hCG, or any combination thereof. Although drawn to DNA arts, the findings in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and Enzo Biochem, Inc. V. Gen-Probe Inc. are relevant to the instant claims. The Federal Circuit addressed the application of the written description requirement to DNA-related inventions in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). The court stated that "[a] written description of an invention involving a chemical genus, like a description of a chemical species, requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." Id. At 1567, 43 USPQ2d at 1405. The court also stated that

> a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA" without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have

> previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is.

Id. At 1568, 43 USPQ2d at 1406. The court concluded that "naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material." Id.

Finally, the court addressed the manner by which a genus of cDNAs might be described. "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." Id.

The Federal Circuit has recently clarified that a DNA molecule can be adequately described without disclosing its complete structure. See Enzo Biochem, Inc. V. Gen-Probe Inc., 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002). The Enzo court adopted the standard that "the written description requirement can be met by 'show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics ....i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. " Id. At 1324, 63 USPQ2d at 1613 (emphasis omitted, bracketed material in original).

The inventions at issue in Lilly and Enzo were DNA constructs per se, the holdings of those cases are also applicable to claims such as those at issue here. A disclosure that does not adequately describe a product itself logically cannot adequately describe a method of using that product.

Thus, the instant specification may provide an adequate written description of hCG for detecting the presence of invasive trophoblast cells or diagnosing quiescent gestation trophoblastic disease, per Lilly by structurally describing a representative number of hCG proteins that can be used for detecting the presence of invasive trophoblast cells or diagnosing quiescent gestation trophoblastic disease or by describing "structural features common to the members of the genus, which features constitute a substantial portion of the genus." Alternatively, per Enzo, the specification can show that the claimed invention is complete "by disclosure of sufficiently detailed, relevant identifying characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics."

In this case, the specification does not describe the hCG proteins that can be used for detecting the presence of invasive trophoblast cells or diagnosing quiescent gestation trophoblastic disease in a manner that satisfies either the Lilly or Enzo standards. The specification does not provide the complete structure of any hCG protein, nor does the specification provide any partial structure of such hCG protein, nor any physical or chemical characteristics of the hCG protein nor any functional characteristics coupled with a known or disclosed correlation between structure and function. Although the specification discloses a single hCG protein that can be used for detecting the presence of invasive trophoblast cells or diagnosing quiescent gestation trophoblastic disease, this does not provide a description of the hCG proteins that can be used for detecting the presence of invasive trophoblast cells or diagnosing quiescent gestation trophoblastic disease that would satisfy the standard set out in Enzo.

The specification also fails to describe the hCG protein that can be used for detecting the presence of invasive trophoblast cells or diagnosing quiescent gestation trophoblastic disease by the test set out in Lilly. The specification describes only that total hCG protein can be used for detecting the presence of invasive trophoblast cells or diagnosing quiescent gestation trophoblastic disease. Therefore, it necessarily fails to describe a "representative number" of such species. In addition, the specification also does not describe "structural features common to the members of the genus, which features constitute a substantial portion of the genus."

Thus, the specification does not provide an adequate written description of the hCG proteins that can be used for detecting the presence of invasive trophoblast cells or diagnosing quiescent gestation trophoblastic disease that is required to practice the claimed invention.

17. All other objections and rejections recited in Office Action of May 30, 2006 are withdrawn.

18. No claims allowed.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Peter J. Reddig whose telephone number is (571) 272-9031. The examiner can normally be reached on M-F 8:30 a.m.-5:00 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley can be reached on (571) 272-0890. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Peter J. Reddig, Ph.D.
Examiner
Art Unit 1642

SUSAN UNGAR, PH.D
PRIMARY EXAMINER

PJR